On page 13, delete the 3rd and 4th paragraphs, and replace these paragraphs with following in accordance with 37 CFR § 1.121. A marked up version showing changes made is attached:

The nucleotide and deduced amino acid sequence of human MKK1, MKK2, and MKK3 are shown in Figures 1A-1B (SEQ ID NOS 1-2), 2A-2B (SEQ ID NOS 3-4) and 3A-3B (SEQ ID NOS 5-6), respectively. Figures 9 (SEQ ID NOS 2 and 7, respectively, in order of appearance), 10A-10B (SEQ ID NOS 4, 8-10, respectively, in order of appearance) and 11A-11D (SEQ ID NOS 6, 11-19, respectively, in order of appearance) show the shared sequence homology between MKKs and related tyrosine kinases.

B2

5.1 The MKK Coding Sequences

The nucleotide coding sequence and deduced amino acid sequence of the human MKK1, MKK2, and MKK3 genes are depicted in Figures 1A-1B (SEQ ID NOS 1-2), 2A-2B (SEQ ID NOS 3-4) and 3A-3B (SEQ ID NOS 5-6), respectively. In accordance with the invention, any nucleotide sequence which encodes the amino acid sequence of an MKK gene product can be used to generate recombinant molecules which direct the expression of an MKK.

On pages 13-14, delete the last paragraph, and replace this paragraph with the following in accordance with 37 CFR § 1.121. A marked up version showing changes is attached:

In a specific embodiment described herein, the human MKK1, MKK2, and MKK3 genes were isolated by performing polymerase chain reactions (PCR) in combination with two degenerate oligonucleotide primer pools that were designed on the basis of highly conserved sequences within the kinase domain of receptor tyrosine kinases

B3

corresponding to the amino acid sequence HRDLAA (residues 350-355 of SEQ ID NO: 2) (sense primer) and [SDVWS/FY] SDVWSF/Y (SEQ ID NO:24) (antisense primer) (Hanks *et al.*, 1988). The MKK cDNAs were synthesized by reverse transcription of poly-A RNA from the human K-562 cell line, ATCC accession number CCL 243, or from the Meg 01 cell line, (Ogura *et al.*, Blood 66: 1384 (1985)).

On page 14, delete 1st paragraph, and replace this paragraph with the following in accordance with 37 CFR § 1.121. A marked up version showing changes is attached:

The PCR fragments were used to screen a lambda gt11 library of human fetal brain. For each individual MKK, several overlapping clones were identified. The composite of the cDNA clones for MKK1, MKK2, and MKK3 are depicted in Figures 1A-1B (SEQ ID NOS 1-2), 2A-2B (SEQ ID NOS 3-4) , and 3A-3B (SEQ ID NOS 5-6), respectively.

On pages 37-38, delete the last paragraph, and replace this paragraph with the following in accordance with 37 CFR § 1.121. A marked up version showing changes made is attached:

cDNA was used in a polymerase chain reaction under standard conditions (*PCR Technology-Principles and Applications for DNA Amplifications*, H.E. Erlich, Ed., Stockton Press, New York 1989). Degenerate pools of primers corresponding to the amino acid sequence HRDLAA (residues 350-355 of SEQ ID NO:2) and SDVWSF/Y (SEQ ID NO:24) were prepared and used for the amplification:

5′ oligo pool

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                H   R   D   L   A   A
5′ GGAATTCC CAC AGN GAC TTN GCN GCN AG 3′ (SEQ ID NO: 20)
               T C   A T C   A   A   C
```

3′ oligo pool

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              F/Y   S   W   V   D   S
5′ GGAATTCC GAA NGT CCA NAC GTC NGA 3′ (SEQ ID NO: 21)
            ATG   CA         C     C
```

Thirty-five PCR cycles were carried out using 8 μg (0.8 μg) of the pooled primers. (Annealing 55°C, 1 min; Extension 72°C, 2 min; Denaturation 94°C, 1 min). The reaction product was subjected to polyacrylamide gelelectrophoresis. Fragments of the expected size (~210 bp) were isolated, digested with the restriction enzyme EcoRI, and subcloned into the pBluskript vector (Stratagene) using standard techniques (*Current*

B5 Cont *Protocols in Molecular Biology*, eds. F.M. Ausubel *et al.*, John Wiley & Sons, New York, 1988).

On page 38, delete the last paragraph, and replace this paragraph with the following in accordance with 37 CFR § 1.121. A marked up version showing changes is attached:

The partial cDNA sequence of the new MKK1 TK, which was identified by PCR, was used to screen a λgt11 library from human fetal brain cDNA (Clontech)(complexity of $1x10^{10}$ recombinant phages). One million independent phage clones were plated and transferred to nitrocellulose filters following standard procedures (Sambrook, H.J., Molecular Cloning, Cold Spring Harbor Laboratory Press, USA, 1989). The filters were hybridized to the EcoRI/EcoRI fragment of clone MKK1, which had been radioactively labeled using 50μCi [α^{32}P]ATP and the random-primed DNA labeling kit (Boehringer Mannheim). The longest cDNA insert of ~3500 bp was digested with the restriction

B6 enzymes EcoRI/SacI to obtain a 5' end probe of 250 bp. This probe was used to rescreen the human fetal brain library and several overlapping clones were isolated. The composite of the cDNA clones of MKK1, MKK2 and MKK3 is shown in Figures 1A-1B (SEQ ID NOS 1-2), 2A-2B (SEQ ID NOS 3-4) and 3A-3B (SEQ ID NOS 5-6), respectively. The 1.75 million independent phage clones of a human placenta library, λZAP, were plated and screened with the 5' end probe (EcoRI/SacI) of the clone used above. Subcloning of positive bacteriophages clones into pBluskript vector was done by the *in vivo* excision protocol (Stratagene).

On page 39, delete the 2nd paragraph, and replace this paragraph with the following in accordance with 37 CFR § 1.121. A marked up version showing changes is attached:

B7 The composite cDNA sequence and the predicted amino acid sequence of MKK1, MKK2 and MKK3 are shown in Figures 1A-1B (SEQ ID NOS 1-2), 2A-2B (SEQ ID NOS 3-4) and 3A-3B (SEQ ID NOS 5-6), respectively.

On page 41, delete the 1st paragraph, and replace this paragraph with the following in accordance with 37 CFR § 1.121. A marked up version showing changes is attached: